Severe neurotoxic envenoming by the Malayan krait Bungarus candidus (Linnaeus): response to antivenom and anticholinesterase

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Abstract

Five patients were bitten by the Malayan krait Bungarus candidus (Linnaeus) in eastern Thailand or north western Malaya. Two patients were not envenomed but the other three developed generalised paralysis which progressed to respiratory paralysis in two cases, one of which ended fatally. One patient showed parasympathetic abnormalities. Anticholinesterase produced a dramatic improvement in one patient. Another patient probably benefited from paraspecific antivenom.

The efficacy of antivenoms and adjuvants such as anticholinesterases in patients with neurotoxic envenoming requires further study.

Introduction

Venoms of kraits (genus *Bungarus*) have attracted much interest among neuropharmacologists since the discovery that bungarotoxins interfere with transmission at the neuromuscular junction.[1] Kraits are common in many Asian countries yet the reported incidence of bites is low. In the few published reports mortality has been high—77% in 35 cases of *B caeruleus* bite in India,[2] 23% in 925 cases of *B multicinctus* bite in Taiwan.[3] The Malayan krait *B candidus* is common in south east Asia, ranging from Thailand to China and south to Indonesia,[4] but clinical reports of proved bites by *B candidus* have not been published. (Older published work is confusing because the common Indian krait *B caeruleus* is sometimes incorrectly referred to as *B candidus*.[4]) We report the cases of five patients bitten by *B candidus* and their response to antivenom and anticholinesterase drugs.

Case histories

CASE 1

A 13 year old Thai boy was bitten on the thigh at 3 am while sleeping on the floor of a hut in Chantaburi region, eastern Thailand. The snake was an 1100 mm long *B candidus*. (The specimen is deposited in the British Museum (Natural History), London, accession No 1982.457.) Within half an hour there was slight swelling, redness, and numbness, but no pain, at the site of the bite and abdominal discomfort. At the health station three hours after the bite he was breathless and unable to open his mouth or swallow. Doses of 20 ml non-specific antivenom, 8 mg dexamethasone, and 0·5 mg atropine were given intravenously. At four hours he could not breathe and was intubated and ventilated manually.

On admission to Pra Pokklao Hospital, Chantaburi, seven and a half hours after the bite the patient was fully conscious but almost completely paralysed and had bilateral ptosis. He replied to questions by flexing fingers and toes. When manual ventilation was stopped briefly he became distressed, sweaty, and cyanosed. The site of the bite was slightly tender but not swollen and showed the imprint of fangs and teeth. The pulse was 120/min and regular and blood pressure 140/70 mm Hg. The abdomen was moderately tender. There was flaccid tetraparesis with total bilateral external ophthalmoplegia, pronounced ptosis, inability to open the mouth, protrude the tongue, or swallow, and no gag reflex (table). Tendon and abdominal reflexes were absent. Manual ventilation, performed by relatives and nurses, was required for a total of 49 hours. On the third day after the bite the eyes were divergent but capable of slight movement in the horizontal plane and downward but not upward. Ptosis hooded two thirds of the pupil.

Summary of clinical findings in three patients envenomed by Bungarus candidus

	Case 1*	Case 2*	Case 3*
Swelling at site of bite	−	−	−
Ptosis	+	+	+
Ophthalmoplegia	+	0	+
Paralysis of jaw, tongue, and deglutition	+	+	+
Respiratory paralysis	+	+	−
Tetraparesis	+	0	+
Parasympathetic abnormalities	+	0	0
Muscle tenderness	−	−	+
Response to non-specific antivenom	−	0	+
Response to anticholinesterase	+	0	−
Polymorphonuclear leucocytosis	+	+	+

* + = Present. − = Absent. 0 = Uncertain or not tested.

On admission the pupils had been fixed and dilated but the patient could see. Pupillary constriction induced by pilocarpine eye drops was tested over a range of concentrations from 0·04% to 4·0% and was considerably reduced on day 3 compared with one month later. While the patient was paralysed the pulse rate was continuously above 120/min. There was sweating and increase in pulse rate in response to difficulties with the airway. There was no reduction in heart rate or blood pressure with changes in position or massage of the carotid sinus. Normal responses were elicited when the patient was reinvestigated one month after the bite. Heart rate rose from 122 to 133 beats/min after intravenous atropine 0·6 mg. Lacrimation and salivation appeared to be normal and bowel sounds were audible.

Laboratory investigations—On admission there was a neutrophil leucocytosis (90% of $22{\cdot}4\times10^9$ cells/l), which subsided within the next four days. Results of biochemical and haematological investigations, including tests of blood coagulation, remained normal throughout. Using an enzyme linked immunosorbent assay[5] *B candidus* venom antigen equivalent to 100 μg venom/l was detected in the serum 15 hours after the bite, but not earlier or subsequently. Antigen was not detected in urine. Specific *B candidus* venom antibody was found in serum five weeks after the bite. The patient could breathe unassisted by the third day, and therafter a gradual increase in muscle power was evident, distal groups improving more rapidly than proximal ones. He was considered completely normal on the 14th day.

Treatment—Doses of 50 ml and 100 ml of Thai Red Cross Society monospecific banded krait (*B fasciatus*) antivenom were infused 12 and 20 hours after the bite without response. On the third day 10 mg edrophonium was given intravenously after 0·6 mg atropine. There

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was an immediate improvement in ptosis, eye movements, and ability to open the mouth and protrude the tongue. The mean time before the lid dropped to hood more than half of the pupil during attempted upward gaze was prolonged from 28 to 70 seconds. The range of eye movements was increased bilaterally by 35° in the horizontal plane and 30° in the vertical plane. Contraction of intercostal and accessory muscles of respiration could be seen and felt for the first time and the sustained maximum expiratory pressure increased from 0·5 to 1·6 kPa (4 to 12 mm Hg). The pressure generated by gripping and by plantar flexing against a partially inflated sphygmomanometer cuff increased by 25% and 20% respectively. These improvements had disappeared 30 minutes later but were restored by a continuous infusion of neostigmine (0·5 mg/h) given with atropine (0·15 mg/h). Deterioration was noted after stopping the infusion six hours later, with improvement on restarting and continuing for 24 hours.

CASE 2

A 44 year old woman who slept on the floor of a rice mill near Chantaburi was bitten on the big toe at 3 am by what she thought was a skink (*Mabuya multifasciata*). The only immediate symptoms were slight local pain and bleeding. She awoke again 30 minutes later breathless and with numbness of the bitten toe and foot. In hospital 35 minutes later she complained of difficulty with breathing and inability to open her mouth.

Examination (table) showed ptosis, tachycardia, and a normal blood pressure. Two hours after the bite she complained of blurred vision and generalised numbness in addition to increasing breathlessness. Two hours later she suffered a respiratory and cardiac arrest from which she was resuscitated but required artificial ventilation. When we first saw her, 14 hours after the bite, there was a single puncture mark on the toe. Anoxic brain death was suspected and she died three hours later.

Laboratory investigations showed a polymorph leucocytosis (93% of $13{\cdot}3 \times 10^9$ cells/l). *B candidus* venom antigen (equivalent to 200 μg venom/l) was detected in tissue fluid aspirated from the bite site.

CASE 3

A 39 year old Chinese man was bitten on the ankle at 3 30 pm while farming in Kedah, Malaya. The snake was a 520 mm long *B candidus*. He walked home, and two hours later headache and giddiness were soon followed by difficulty in keeping his eyes open and swallowing. Pains in the trunk and limbs started four and a half hours after the bite. Movement aggravated the pains, which progressively increased precluding sleep. He was admitted to Penang General Hospital 19 hours after the bite. On examination fang marks were evident but there was no swelling, discoloration, or tenderness at the site of the bite or of regional lymph nodes. He was conscious and responded by grunts or slight hand movement. Pulse was 90/min, respiration 25/min, and blood pressure 130/70 mm Hg. There was bilateral ptosis, total external ophthalmoplegia, and paralysis of facial muscles (table). Maximal jaw opening was 1 cm between teeth margins. He could not protrude his tongue or swallow. Pupillary responses were normal. There was generalised paresis. All muscles were tender, and passive movements were very painful. Fasciculations were evident in the legs. Tendon and plantar reflexes and sensation appeared normal.

Treatment—Intravenous infusion of 100 ml Haffkine polyspecific (*B caeruleus, Echis carinatus, Vipera russelli, Naja naja*) antivenom was started 20 hours after the bite. Within five minutes an anaphylactoid reaction developed but responded promptly to adrenaline, after which the antivenom infusion was completed in 30 minutes. One hour after starting antivenom the patient indicated that he felt much better, and four hours later there was clear objective improvement. Eye movements had returned to 75% of normal, ptosis to 25% normal, maximal jaw opening was 3 cm between teeth margins, and he could protrude his tongue 2 cm beyond teeth margins. Hand grips were stronger and pains on muscle movement seemed less severe. He could lift his head and heels off the bed for a few seconds. At seven hours after antivenom he could swallow; 22 hours after antivenom (42 hours after the bite) eye movements were normal but ptosis was unchanged, jaw opening was 2·2 cm, and tongue protrusion was also 2·2 cm. Head raising was 50% of normal and he was just able to turn on to his side. Forty eight hours after the bite 1 mg neostigmine was injected subcutaneously after 0·6 mg atropine. He "felt better" but there was no objective improvement in muscle power during the subsequent three hours. Three days after the bite he could walk though was still unable to sit up in bed unaided. Pains on muscle movement were minimal. Jaw opening (5 cm), tongue protrusion (3 cm), speech, and swallowing were normal. Thereafter limb and trunk power improved to complete recovery six days after the bite.

Investigations—On admission the white blood cell count was $17{\cdot}4 \times 10^9$/l (90% neutrophils) and became normal three days later. Other haematological indices and clot quality remained normal. Results of urine analysis were normal. Serum aspartate and alanine transaminase activities were initially normal, but alanine activity rose to a peak of 128×10^3 U/l seven days after the bite, falling to normal (below 45×10^3 U/l) in four days. Aspartate transaminase activities remained normal (below 42×10^3 U/l) except for a value of 55×10^3 U/l five days after the bite. Other biochemical values were normal.

CASES 4 AND 5

An 11 year old girl was bitten at 4 am by a 1400 mm long *B candidus* (British Museum (Natural History) accession No 1982.458) near Chantaburi, and a 47 year old Chinese man was also bitten at 4 am by an 1100 mm specimen of the same species in Kedah. Neither patient developed evidence of envenoming.

Discussion

This series shows that *B candidus* can cause severe neurotoxic envenoming in man. Like the Indian krait *B caeruleus*[2] and the African spitting cobras,[6 7] *B candidus* usually bites at night while the victims are asleep at home. The incidence of *B candidus* bites has probably been underestimated, and immunodiagnostic methods (see case 2) may confirm a higher incidence of envenoming by this species. Two patients (cases 4 and 5) were bitten by large snakes yet showed no evidence of poisoning, re-emphasising that highly venomous species may bite without injecting venom.

The preparalytic phase may be as long as 12 hours after krait bites,[2 8] although in our cases paresis started between 75 minutes and three hours after the bite. Local effects were negligible. In cases 1, 2, and 3 there was virtually complete neuromuscular paralysis, proceeding in cases 1 and 2 to respiratory failure. The survival with complete recovery in case 1 illustrates the value of prolonged assisted ventilation,[9 10] particularly when effective antivenom is not available. The abnormalities in the parasympathetic nervous system in case 1 suggest that krait venoms have cholinergic blocking activity[8] apart from familiar effects on neuromuscular transmission. In case 3 the generalised pains on muscle movement resembled those in patients envenomed by sea snakes[11] and Australian land snakes.[12] Generalised rhabdomyolysis was excluded, however, by normal serum creatinine and aspartate transaminase activities and the absence of myoglobinuria.

In case 1 banded krait (*B fasciatus*) antivenom did not benefit the patient, whereas in case 3 there was significant improvement four hours after Haffkine polyspecific antivenom, although the possibility of spontaneous improvement cannot be excluded. We have tested the ability of four antivenoms to protect mice from the lethal effects of *B candidus* venom. Thai *B fasciatus* and Taiwan *B multicinctus* antivenoms were ineffective. Haffkine antivenom was effective (ED_{50} against 5 LD_{50} venom intravenously, 28 μl/mouse) and Australian tiger snake antivenom was even more effective (ED_{50} 14 μl/mouse).

In case 1 edrophonium produced a dramatic improvement, suggesting that neither the parasympathetic cholinergic nerve terminals nor the motor end plates were completely blocked. Experimentally the neuromuscular blocking activity of snake venom fractions are often reversible by anticholinesterases,[1] whereas the activity of whole venoms is affected much less if at all.[13] Clinical impressions have been both favourable[14 15] and (as in case 3) unfavourable.[8 10 11] We conclude that further critical clinical studies, including objective measurements, are needed both of antivenoms and of adjuvant treatment such as anticholinesterases in neurotoxic envenoming.

We thank Miss Eunice Berry and Miss Jean Taylor for secretarial help and the Wellcome Trust and Medical Research Council for financial support. Studies in Thailand were part of the Wellcome-Mahidol University—Oxford, Tropical Medicine Research Programme.

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(*Accepted 24 December 1982*)

Intramuscular on demand analgesia: double blind controlled trial of pethidine, buprenorphine, morphine, and meptazinol

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Abstract

An on demand intramuscular analgesic system using the Cardiff Palliator was tested. Forty consenting patients were studied after cholecystectomy in a double blind trial using increments of buprenorphine (0·15 mg), meptazinol (50 mg), morphine (5 mg), and pethidine (50 mg). Most patients attained good levels of pain relief (mean analogue pain score 36·5), comparable to intravenous on demand analgesia. There were no technical complications. Significant differences were found between drugs in dizziness (pethidine produced the worst score) but not with other side effects. Buprenorphine produced longer lasting analgesia than meptazinol or pethidine and also gave the lowest pain scores. Patterns of analgesic consumption were the same as with intravenous on demand systems, but larger amounts of drug were generally used. Relative analgesic potencies derived from drug consumption rates were also consistent with those from intravenous on demand studies.

An on demand intramuscular analgesic system offers a simple but effective means of relieving severe post-operative pain.

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Introduction

Routine intermittent intramuscular injections of analgesics administered by nurses do not give good postoperative analgesia,[1] and many other methods of administration have been claimed to give better results.[2-6] Studies on any novel system for dispensing analgesics are apt to yield better results than existing practices by increasing the attention paid to individual patients. The value of any innovation will, however, also depend on implementation and practicality for routine use.

A system combining the simplicity (and acceptability to nursing staff) of intramuscular injections together with the versatility (and intuitive appeal to patients) of an on demand system would seem to have practical advantages.

An initial pilot study showed that repeated injections through an indwelling intramuscular cannula produced little or no discomfort so long as the volume and rate of injection were limited. This study was performed to determine whether an intramuscular on demand system would give good postoperative pain relief without introducing further problems. As the effectiveness of intramuscular analgesics may be influenced by physicochemical factors affecting rate of absorption, four different drugs (buprenorphine, meptazinol, morphine, and pethidine) were studied. Morphine and pethidine have been used in most methods of pain relief so far described; buprenorphine and meptazinol have been studied in intravenous on demand systems.[7 8]

Methods

Forty patients undergoing uncomplicated elective cholecystectomy were studied; they were aged between 18 and 70 years, and none of the women was pregnant. The trial was conducted double blind, patients being allocated at random to receive one of the analgesics for